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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,043	10/21/2003	Matthias Mack	13235-014001	3494

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,043	MACK ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 32-52* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 41-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 32-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 27 April 2007 has been entered in full. Claims 29-31 are canceled. Claims 1-28 and 32-52 are pending. Claims 1-27 and 41-52 are withdrawn. Claims 28 and 32-40 are under examination.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 27 April 2007 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The specification is in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations.

The rejection to claims 28, 30-40 under 35 U.S.C. 112, first paragraph, scope of enablement, as set forth at pages 2-3 of the previous Office Action (27 October 2006), is *withdrawn* in view of the amendment (27 April 2007).

The rejection to claims 28-40 under 35 U.S.C. 112, second paragraph, as set forth at page 7 of the previous Office Action (27 October 2006), is *withdrawn* in view of the amendment (27 April 2007).

Claim Rejections-35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 28, 29 and 32-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bruhl *et al.* (reference of record) in view of Schuh *et al.* (reference of record) and Blease *et al.* (reference of record). The basis for this rejection is set forth at pages 7-11 of the previous Office Action (27 October 2006).

Applicant cites MPEP 2143 and *In re Vaeck*, 947 F.2d 488,493 (Fed. Cir. 1991). Applicant states that Bruhl report studies of a RANTES-PE38 fusion protein and its effect on CCR5+ CHO cells *in vitro*. Bruhl concludes that the CCR5+ cells internalize the fusion protein, and that the PE38 toxin retains its cytotoxic activity, killing the cells. Applicant states that the authors suggest that the fusion protein may be useful for treating chronic inflammatory diseases. Applicant argues that nothing in Bruhl teaches or suggests the use of a RANTES-PE38 fusion protein for the treatment of allergic asthma as recited in the claims. Applicant states that Schuh teaches a method in which anti-RANTES antibody is used for treating allergic asthma and that anti-RANTES antibodies curtailed leukocyte and eosinophil recruitment in mice, concluding that neutralization of RANTES/CCL5 further reduced the hallmarks of allergic asthma. Applicant argues that the Examiner asserts that it would have been obvious to one of ordinary skill in the art to use the RANTES-PE38 fusion protein in combination with anti-

RANTES antibodies described in Schuh to treat allergic asthma. Applicant argues that administration of a RANTES-PE38 fusion protein, as in the pending claims, activates RANTES receptors. Applicant argues that this is confirmed by studies demonstrating that upon the administration of a RANTES-PE38 fusion protein, more macrophages and eosinophilic granulocytes were detected in the lung. Applicant submits that the RANTES-PE38 fusion protein elicits its biological effects not by neutralization of RANTES, as would the anti-RANTES antibody described in Schuh, but by activating RANTES receptors and depleting certain RANTES-PE38 sensitive cells. Applicant maintains that Bruhl discloses that a therapeutic benefit is achieved by administering a RANTES polypeptide, whereas Schuh discloses that a therapeutic benefit is achieved by neutralizing RANTES using a RANTES antibody. Applicants therefore assert that one skilled in the art would not be motivated to combine a RANTES-PE38 fusion protein, with an anti-RANTES antibody, especially given the findings that the RANTES-PE38 fusion protein increases macrophages and eosinophilic granulocytes and, in contrast, the anti-RANTES antibody curtailed leukocyte and eosinophil recruitment. Applicant maintains that for these reasons, neither the teachings of Bruhl or Schuh either alone or in combination would lead one of skill in the art to administer such a chimeric polypeptide for the treatment of allergic asthma as recited in the claims. Applicant argues that Blease (reference of record) does not remedy the shortcomings of Bruhl and Schuh, because Blease makes no connection between CCR5, allergic asthma and the reduction of macrophages.

Applicant's arguments have been fully considered but are not deemed persuasive. Firstly, the Examiner DID NOT state, "it would have been obvious to one of ordinary skill in the art to use the RANTES-PE38 fusion protein in combination with anti-RANTES antibodies described in Schuh to treat allergic asthma". The Examiner stated, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the anti-CCR5-anti-CD3-bispecific ab or the chimeric fusion protein RANTES-PE38 to deplete CCR5 expressing cells as taught by Bruhl *et al.* in a method for reducing/depleting macrophages in a human suffering from allergic asthma with a reasonable expectation of success". Please see the previous Office Action (27 October 2006; pages 10-11). Applicant submits that administration of a RANTES-PE38 fusion protein, as in the pending claims, activates RANTES receptors. Applicant argues that the RANTES-PE38 fusion protein elicits its biological effects not by neutralization of RANTES, as would the anti-RANTES antibody, but by activating RANTES receptors and depleting certain RANTES-PE38 sensitive cells. Bruhl *et al.* teach that the CCR5 receptor is expressed on monocytes/macrophages and T cells. Bruhl *et al.* teach **the depletion of CCR5-positive primary monocyte cells using anti-CCR5-anti-CD3-bispecific antibodies** *in vitro*. Bruhl *et al.* teach that the **RANTES-PE38 fusion protein binds to CCR5 and down modulates the receptor from the cell surface of primary monocytes, lymphocytes and T cells *in vitro*. Bruhl et al. teach that RANTES-PE38 fusion protein binds and destroys CCR5-positive CHO cells *in vitro*.** Bruhl *et al.* teach that the construct efficiently depletes CCR5 positive cells and appears useful as an agent in the treatment of chronic inflammatory disease and is a promising candidate

as a therapeutic agent. Schuh *et al.* teach a correlation between CCR5 receptor and allergic asthma. **Individuals who are homozygous for the coding sequence of CCR5 are highly resistant to asthma**. Schuh *et al.* teach that **the lack of CCR5 receptor markedly restricted the development of fungal asthma** and that the neutralization of RANTES (via administered anti-RANTES antibodies) further reduced the hallmarks of allergic asthma in the mouse model. Both references provide suggestion/motivation to modify the combined reference teachings to make the instant invention and provide a reasonable expectation of success. Bruhl and Schuh teach the CCR5 receptor as a key contributor to the development and maintenance of asthma using experiments that demonstrate that **RANTES-PE38 fusion protein binds to CCR5-positive cells, down modulates the receptor from the surface and destroys the cells *in vitro*** and experiments that teach that **the lack of CCR5 receptor markedly restricted the development of fungal asthma in a mouse model**. Based on the teachings, it would be obvious to use a composition that inhibits the signal transduction pathway via the CCR5 receptor. The Blease et al. reference was submitted because it teaches that IL-13 contributes to allergic and asthmatic responses and that a chimeric fusion protein comprising IL-13 and Pseudomonas exotoxin (IL-13-PE38QQR) ameliorated chronic fungal-induced allergic airway disease in the mouse model.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action.

In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
7/12/07

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER

AU1647 7/17/07